Detection of Placental Lesions in Fetal Growth Restriction

Dinesh Shah, MD, Professor – Principal Investigator
University of Wisconsin, School of Medicine and Public Health
Department of Obstetrics and Gynecology
202 S. Park St.; Madison, WI 53715
dmshah@wisc.edu
(608) 417-6099

Oliver Wieben, PhD, Associate Professor – Co-Principal Investigator
University of Wisconsin, School of Medicine and Public Health
Department of Medical Physics
1111 Highland Ave.; Madison, WI 53705
owieben@wisc.edu
(608) 263-0793

Dr. Kathleen Antony, MD, Associate Professor – Clinical Investigator
University of Wisconsin, School of Medicine and Public Health
Department of Obstetrics and Gynecology
202 S. Park St.; Madison, WI 53715
dmshah@wisc.edu
(608) 417-6099

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ICTR Data Monitoring Committee Contact: Amy Siedschalg, MS
University of Wisconsin, School of Medicine and Public Health

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Study Location:

UnityPoint-Meriter Hospital
202 South Park Street
Madison, WI 53715

Wisconsin Institutes for Medical Research (WIMR)
1111 Highland Avenue
Madison, WI 53706

UW Radiology MRI Facility
1. S. Park Street
Madison, WI 53715

Ian Bird Laboratory
202 South Park Street
Madison, WI 53715

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Statement of Compliance

The signature below constitutes that the research will be conducted in accordance with the approved protocol, applicable regulations, laws and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Dinesh M. Shah, M. D._____
Printed Investigator Name

_____ _____
Investigator Signature Date

Abbreviations

ASL: arterial spin labeling

BMI: body mass index

BOLD: blood oxygenation level dependent

DCE: dynamic contrast enhanced

DMC: data monitoring committee

FE: ferumoxytol

FGR: fetal growth restriction

GA: gestational age

ICTR: Institute for Clinical & Translational Research

IVIM: intravoxel incoherent motion

MFI: maternal-fetal interface

MFM: Maternal and Fetal Medicine

MRI: magnetic resonance imaging

NB: newborn

NHP: non-human primate

PC VIPR: phase contrast vastly-under-sampled isotropic projection imaging

PE: pre-eclampsia

RF: radiofrequency

SAR: specific absorption rate

SMS: Study Monitoring Service

UPBF: uteroplacental blood flow

U/S: ultrasound

VI: vascularization index

FI: flow index

VFI: vascularization flow index

VS-ASL: velocity selective-arterial spin labeling

2D PC: two dimensional phase contrast

4D: four dimensional

BACKGROUND

The majority of pregnancy complications have their origins in vascular maladaptation resulting in reduced perfusion, and are commonly associated with altered uteroplacental inflammation, immune cell homing and/or activation, all of which are further exacerbated by the greater level of hypoxia at the maternal-fetal interface (MFI). Suboptimal placentation is often accompanied by FGR with or without hypertension. There is a clear need for non-invasive assessment of vascular function and inflammation at the MFI, including in early pregnancy to identify any of these developing pathophysiologic conditions before their clinical manifestation. With adverse pregnancy outcomes, inappropriate growth factor and/or cytokine profiles, whether of immune cell, placental or maternal (including vascular) origin, play roles in the development of these outcomes.

Underlying vascular deficits eventually lead to pathological findings in the placenta that include acute atherosis (vascular lesions), placental infarcts with fibrosis (white infarcts) or without fibrosis (red infarcts) and perivillous fibrin deposition. Placental infarcts are preceded by formation of intervillous clot formation. These placental lesions identified after delivery are similar in FGR and preeclampsia. Diagnosis of FGR at early stages of pregnancy, generally at or before 26 weeks gestation have higher likelihood of underlying genetic cause or fetal viral infection. Early FGR of genetic etiology may be characterized by congenital defects frequently detected by ultrasound. FGR or viral etiology may be characterized by intracranial or intraabdominal echogenecity. FGR diagnosed later in gestation is more likely to be due to placental lesions. However, such clinical diagnosis of FGR is in error 60% of the time. (Review of our own data here at UW-Unity Point Health-Meriter) Identifying the placental lesions and detecting macrophage recruitment at placental implantation site in the uterine wall will improve the accuracy of the diagnosis of FGR and is likely to provide information on immune activation, which will identify individuals who will subsequently develop preeclampsia.

Currently there are no reliable methods for identifying these lesions during pregnancy. Therefore, developing imaging methods for identifying placental lesions and macrophage recruitment during pregnancy in FGR would advance diagnostic methodology for both FGR and preeclampsia, which may potentially allow interventions in the future. Perivillous fibrin deposition is preceded by reduced intervillous blood flow and subsequently will alter intervillous flow patterns, to be detected by MRI. Extensive perivillous fibrin deposition with further reduction in blood flow would result in formation of intervillous clot. MRI has much higher degree of tissue resolution, which would allow us to detect intervillous clot formation, identify regional reduced placenta perfusion and decrease placental oxygenation (BOLD). We posit that MRI techniques can identify these lesions with high degree of resolution and hence accuracy.

Ultrasound

The current obstetrical workup of patients using advanced U/S methods includes assessment of fetal growth, Doppler interrogation of the uterine artery for vascular resistance and detection/resolution of diacrotic notching, and fetal umbilical artery Doppler for placental vascular resistance. Advances in technology allow for measurements of regional flow in arteries of diameters as small as 0.75 mm [5]. Currently

specificity of uterine artery Doppler interrogation is limited for prediction of either FGR or PE [6-22], and fetal umbilical artery Doppler is good only at late stages of fetal hypoxemia. Finite limits in U/S resolution, inability to identify altered oxygen tension, and a paucity of techniques to identify immune cell homing restrict our ability to identify the developing pathophysiologic conditions mentioned above upon or before their clinical manifestation. In addition, obesity is a particularly relevant environmental condition wherein we know there is an increased risk of complications, and yet obesity in itself can pose a challenge to current U/S imaging techniques further limiting our ability to assess these conditions.

Most importantly, technical resolution of ultrasound is quite limited for detection of placental lesions (White or red infarcts or perivillous fibrin deposits or intervillous clot formation) in FGR and preeclampsia. Ultrasound certainly cannot detect macrophage recruitment in the uterine wall.

Magnetic Resonance Imaging

MRI can probe vascular function and health, including flow, perfusion, and oxygenation mapping. Complications in imaging the placenta include 1) motion artifacts (mother's breathing, fetal body motion, cardiac motion, and pulsatility of two cardiovascular systems); 2) the small size of the placental vessels and 3) safety concerns for the fetus regarding energy deposition characterized by the specific absorption rate (SAR) as well acoustic noise in the last trimester. Consequently, MRI performed during the first trimester is usually limited to maternal indications only. There are no reports that MRI is unsafe for the fetus or the mother, but no dedicated safety studies have been conducted and the current models used to predict thermal effects from SAR are primitive. Emerging data on human MRI performed for clinical indications strongly suggest lack of fetal harm from SAR and from noise. Human studies in this proposal follow all safety guidelines and are limited to the late second and/or third trimester.

Our primate study investigated MRI in the first trimester and it has been shown to be clinically informative, and further placate SAR safety concerns. The rhesus macaque (Macaca mulatta) has significant advantages as an experimental model, including a villous organization of the placenta, extensive extravillous trophoblast invasion and remodeling of the decidual spiral arteries, and a first trimester decidual leukocyte population very similar to the human.[26, 27] Thus, the rhesus provides an ideal opportunity to develop imaging modalities in the very earliest stages of gestation, which are not accessible in human pregnancy, as well as throughout all of pregnancy. Our ferumoxytol infusion study in rhesus macaque provides significant reassurance for late second trimester MRI and demonstrates lack of any fetal safety concern from Ferumoxytol infusion. * All MRI sequences have lowered SAR thresholds for higher safety margins and will incorporate methodology to reduce motion artifacts.

Perfusion and Oxygenation

Perfusion is a vital function of the healthy placenta and low perfusion is an indicator of insufficient vascular remodeling and/or the formation of intervillious thrombi [32, 33]. Significant perfusion deficit impedes oxygen exchange and so placental function. Utilizing power Doppler ultrasound, placenta perfusion metrics have been derived non-

invasively in third trimester pregnancies (vascularization index [VI], flow index [FI], and vascularization flow index [VFI]) [34, 35], but the intra and inter observer reproducibility of these metrics is limiting [36, 37]. In particular, these metrics are highly sensitive to system based parameters (e.g. gain) and those imposed by the variable acoustic windows of patients (e.g. attenuation) [38].

The use of MRI for perfusion assessment offers reduced sensitivity to placenta geometry and potentially improved reproducibility. MRI provides multi TE gradient echo sequence which is BOLD dependent. We will apply several non-contrast techniques we investigated for the measurement of perfusion and have optimized for the placenta. The performance of these techniques was directly compared (initially in a non-human primate model) to dynamic contrast enhanced MRI (DCE) utilizing ferumoxytol (Fe) as a contrast agent for DCE (SA 3). (SA 3 and 4). Here we propose to use DCE techniques using ferumoxytol to cases of FGR.

We posit that non-contrast MRI will provide limited information on placental perfusion and help identify areas of perfusion deficits due to intervillous clot formation due to detailed tissue architecture information. Furthermore, villous tissues surrounding these clots are expected to have significant oxygen deficit as compared to functionally active areas of placenta, which then allows with BOLD information to validate detection of intervillous clots. Similarly, placental infarcts have different tissue architecture and low oxygen saturation allowing these to be detected by stepwise application of tissue analysis followed by BOLD application. As much as ASL may not be sensitive in of itself to detect perfusion deficits, comparison of various intervillous flow patterns may allow detection of perfusion deficit areas, which can be further refined by application of BOLD analysis.

Inflammation

Gadolinium (Gd) based contrast agents for MRI can be used for imaging of inflammation,[39] but have teratogenic potential and are generally contraindicated during pregnancy because they cross the placenta. Ferumoxytol is a superparamagnetic iron oxide (SPIO) designed for the treatment of anemia, especially for renal deficiency cases. Anemia in the mother during pregnancy is a common problem and if oral iron cannot correct deficiency, physicians frequently use parenteral iron preparations. Since ferumoxytol is a relatively newer formulation, there is very limited experience of using it during pregnancy, we are not aware of published reports. Ferumoxytol has been approved for treatment of anemia refractory to conventional oral therapy and for use in pregnancy for refractory anemia. * However, given the safety profile of ferumoxytol compared to existing agents, we are inclined to switch over to using ferumoxytol when any future needs for clinical use of parenteral iron arises in our clinic. It also has unique MRI related properties including regional T1 and T2* shortening. Importantly, ferumoxytol delivers iron to macrophages by phagocytosis with highest density in the reticuloendothelial system, but can be taken up by those cells mobilized as part of an inflammatory response.

In recent decades it has become clear that the endometrium has a novel immune environment [40], with natural killer (NK) cells [41] being the predominant decidual leukocyte in the first trimester, prominent populations of macrophages, and smaller numbers of T-reg lymphocytes [40, 42]. Early pregnancy has been proposed as a sterile proinflammatory environment [43], and there is some evidence that endometrial inflammation promotes improved embryo implantation. As pregnancy progresses, secretion of proinflammatory cytokines by decidual macrophages at term is thought to contribute to the onset of myometrial contractions and parturition [44]. Thus, early and late pregnancy have been proposed to be proinflammatory environments [43], although current approaches are unable to determine in real time the inflammatory cell populations at the maternal-fetal interface. Elevated decidual macrophage densities have been noted in third-trimester histological specimens from PE pregnancies in some [45] but not all studies [46, 47]. We hypothesize that uptake of ferumoxytol by decidual macrophages will allow us to use Fe-MRI to localize and potentially quantify these inflammatory cells in the decidua, and assess any changes with pregnancy condition.

Ferumoxytol

Feraheme® (ferumoxytol) infusion is an iron replacement product currently FDA approved for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have chronic kidney disease (CKD). To the best of our knowledge ferumoxytol is the only intravenous iron preparation that was used to localize macrophages at the site of homing in human beings. Ferumoxytol has also been investigated as an alternative in magnetic resonance angiography (MRA) for individuals who are allergic to conventional contrast agents.

Decreased uteroplacental perfusion is a recognized antecedent event in pregnancies that ultimately result in adverse outcomes like fetal growth restriction, preeclampsia and/or preterm birth. This concept is well supported clinically by identification of spiral artery vascular lesions called acute atherosis in the placenta after delivery. Current literature suggests that vascular adaptation events occur very early in pregnancy, which is why we have used multiple imaging techniques related to blood-flow at early time points in gestation in the main U01 project. We propose that individuals with either poor maternal vascular response and/or inadequate spiral artery remodeling with resultant inadequate placentation will have a reduced uteroplacental blood-flow and perfusion. Given that the spiral arteries draw the vast majority of the blood flow supplied to the uterus in a gravid state, poor placentation would be reflected in reduced total uteroplacental blood flow.

If the uteroplacental blood-flow/perfusion deficiency persists into later stages of pregnancy, current literature suggests that there is activation of an inflammatory state with homing of immune cells, specifically macrophages, in the decidua at the site of placental implantation (decidua basalis). Recently, scientists have described identification of macrophages by their uptake of iron particles following infusion of ferumoxytol in patients recently diagnosed with type I diabetes with an inflammatory state in the human pancreas. We suggest that by high precision 3-D mapping we should

also be able to identify homing of activated macrophages in the decidua basalis. We have recently received FDA IND for use of Ferumoxytol for placenta imaging as proposed in the main U01 placenta imaging project (see copy of IND application and FDA letter confirming receipt of application and outlining and email communication). An IND amendment will be submitted to the FDA before implementation of the FGR sub-project.

Overall, the objective of this sub-project is to develop imaging methods to diagnose **placental lesions** in an on-going pregnancy, detect macrophages and correlate them with placental pathology findings. FGR and preeclampsia have similar placental pathological lesions seen on examination of placenta after delivery. In order to avoid subjecting patients with evolving or mild preeclampsia to noise in the MRI machine, we propose to study subjects with FGR with high likelihood of placental lesions. Methodology would then be applicable for all cases at risk as long as it is clinically safe to perform such imaging.

FGR is generally diagnosed in late second and in third trimester of pregnancy. We propose to study subjects with early third trimester (between 27 0/7-32 6/7 weeks) diagnosis of FGR. These cases of FGR have higher likelihood of being due to placental lesions than those diagnosed in second trimester and even higher likelihood of placental lesions than those diagnosed in late third trimester (33-38 weeks). Late FGR (33-38 weeks) also has higher likelihood of having evolving preeclampsia. Early third trimester (27 0/7-32 6/7 weeks) cases also have higher likelihood of underlying or overt vascular dysfunction. These subjects are then ideal for the purpose of our investigation proposed herein.

Framework for selection of FGR cases: A substantial percentage (40% based on our own data) of FGR cases are simply constitutionally small fetuses, i.e. not diagnosed as FGR by post-natal evaluation by pediatricians. The three clinical etiologic causative subsets of non-constitutional FGR diagnosed in early third trimester are:
1. Genetic etiology: Chromosomal disorders or single gene disorders. If there are no fetal structural malformations diagnosed by ultrasound, the patient has had a prenatal genetic screening test that showed her to be low-risk for genetic disorder and the FGR diagnosis is made after 26 weeks, the likelihood of genetic etiology for FGR is low.
2. Viral syndrome: If ultrasound examination does not reveal any intracranial or intra-abdominal calcifications and TORCH testing (optionally performed, by patient choice, at diagnosis of FGR) does not indicate recent viral infection cause for FGR and FGR diagnosis is made after 26 weeks, the likelihood of FGR of viral etiology is low.
3. Placental cause: The vast majority of FGR cases of placental origin are secondary to reduced uteroplacental flow and perfusion, are generally diagnosed after 26 weeks gestation and have a high likelihood of placental lesions. This is especially true in settings of underlying vascular dysfunction (preexisting hypertension).

From the clinical point of view, the ability to detect placental malperfusion and to determine the presence of activated macrophages in the decidua basalis would help clinicians to identify the initiation of the disease pathway. This would allow us to confirm

that the pathological state has resulted secondary to reduced uteroplacental perfusion that led to FGR and to be able to detect placental etiology of FGR by visualization of placental lesions will be a substantial progress in the field.

We are requesting IRB approval for FGR sub-project in which we propose to perform contrast MRI with ferumoxytol for flow and perfusion and BOLDT similar to one proposed in the main study and to perform a follow-up MRI after the contrast agent has cleared and ferumoxytol has been picked up by macrophages.

Preliminary data: *Non-human primate (NHP) model*
In year 2, the MR sequences including the ferumoxytol approach were validated in a longitudinal primate study (n=9) throughout gestation, to establish the sensitivity, feasibility, and general safety of imaging in the first trimester for future consideration in humans. We established a non-human primate (NHP) model that will allow us to address safety concerns and guide the further conduct of human studies. We have extensively characterized the histological distribution, phenotype, and function [48] of leukocytes in the macaque decidua and have shown in early pregnancy the dramatic influx of (primarily, innate) immune cells to the maternal-fetal interface [27, 49-51]. We used this expertise to evaluate the primate MFI with ferumoxytol MRI, promoting immune cell homing using intraamniotic IL1β infusion as shown by Persicce [52].

Currently, there is no official registry with data on ferumoxtyol use in pregnant women. However, it is being studied in pregnant women. We have done preliminary studies in a non-human primate model.

STUDY OBJECTIVES AND AIMS

The overall objective of this sub-project is to develop imaging methods to diagnose placental lesions in an on-going pregnancy, detect macrophages and correlate them with placental pathology findings in patients with clinical diagnosis of FGR.

Specific Aim 1 - Ferumoxytol (Fe) MRI
We will pursue two approaches for the detection of ferumoxytol signal: R2* and QSM.

Specific Aim 2 - MR Perfusion and Oxygenation
We will test several approaches for MR perfusion measurements without a contrast agent as well as BOLD imaging for probing placental oxygenation.

RESEARCH DESIGN AND METHODS OVERVIEW

Patients can be diagnosed with FGR anytime between 27 0/7 - 32 6/7 weeks gestation. All patients will be offered participation into the study at the time of FGR diagnosis.

Research Procedure Descriptions

Blood/urine collection for research
Blood and urine samples are collected at the consenting visit and at the time of delivery. A total of 10 mL, of blood is collected via venipuncture along with an aliquot of a urine sample. For research visits that coincide with clinical visits, research blood samples are collected in conjunction with clinical samples, saving subjects an additional needle stick. All subjects are asked if they wish to have left over research samples banked for future unspecified research. Blood and urine samples will be analyzed to monitor relevant maternal growth factors, multiplex assays for Cytokine panel and MMPs. Urine will be tested for Shed VECad.

60 minute MRI:
This MRI scan will take approximately 60 minutes. Prior to entering the MR suite, subjects are screened again for MRI safety and compatibility. The MR imaging exam is expected to take approximately 60 minutes with some additional time to get subjects comfortably placed in the scanner. Subjects are made as comfortable as possible in the bore and are provided with an alarm, which allows them to get the attention of the MR technologist conducting the scan. There is a break between scans to ensure the comfort of the subjects.

Ferumoxytol administration:
The MRI imaging with ferumoxytol as a contrast agent will be conducted at the scheduled visits based on timing of FGR diagnosis. We will administer ferumoxytol in a hospital triage setting with maternal pulse and blood pressure monitoring and fetal heart rate monitoring. The pharmacy will be notified in advance of the arrival of the patient, so that they can prepare the infusion in a timely fashion and deliver it to triage upon patient's arrival. Subjects will arrive at UnityPoint-Health Meriter Hospital obstetric triage unit as prescheduled for ferumoxytol infusion. Later that same day, the subjects will present to the UW Hospital, WIMR or 1 S. Park location for their pre-scheduled MRI. In the triage unit, the nurse will obtain baseline vital signs, including maternal pulse, blood pressure, and fetal heart rate. Following this, the nurse will initiate an infusion dose of ferumoxytol. We plan to administer Ferumoxytol intravenously, by infusion, over 30 minutes. The patients will be monitored at 5 to 15-minute intervals, for pulse, blood pressure, respiration, and fetal heart rate. The MRI scanning procedure will be conducted at the UW Hospital, WIMR or 1 S. Park location for approximately 60 minutes.

The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. We plan to dilute half of the recommended initial dose, i.e. 255 mg in 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. We will give Feraheme only once, in one infusion of 255 mg to each subject who has consented for this study.

2-3 weeks after the ferumoxytol infusion you will be asked to return to Meriter-Hospital for a blood draw to assess your iron levels.

Obtain clinical (obstetric) data from medical records review
All clinical data from prenatal visits including GA specific maternal weight, blood-pressure, urine protein and pregnancy dating, GA at delivery, birth weight, neonatal outcome including routine NB hearing test, data specifically regarding fetal growth restriction (FGR) and maternal complications like PE or hypertension requiring preterm delivery is recorded. We confirm normal outcomes as defined by absence of any clinical (neonatal BW percentile for GA) parameters of diagnosis of FGR and absence of any clinical evidence of PE or superimposed PE by current ACOG criteria.

The patient's clinical provider will be informed that the patient is participating in the FGR study and that, if any unknown conditions or illnesses are identified during the course of prenatal care, we would appreciate knowing from them with patient's consent. We also set up a mechanism in the obstetrics triage unit in the UnityPoint Health-Meriter inpatient facility for all pregnant women admissions to include a specific alert for the nursing staff that the patient is a study participant and that patients should be informed, and, with the patient's permission, study coordinator can be notified for any new conditions and/or illnesses.

SUBJECT POPULATION AND ELIGIBITY CRITERIA

Sample Size
The total sample size is 20.

Inclusion Criteria

1. Pregravid BMI 18.5-39.9 Kg/m^2
2. Women with singleton pregnancies
3. Ultrasound confirmed pregnancy dating prior to 14 weeks gestation
4. Gestational age of 27 0/7 - 32 6/7 weeks at FGR diagnosis based on standard clinical criteria.
    a. Estimated Fetal Weight: less than 10 percentile OR
    b. abdominal circumference less than 10^{th} percentile

Exclusion Criteria

1. Diagnosis of preeclampsia at FGR diagnosis
2. Gestational Diabetes Mellitus or type I/II Diabetes Mellitus
3. Known fetal chromosome abnormality, structural malformation or syndromes in current pregnancy
4. Known fetal viral infection syndrome
5. Alcohol/drug/tobacco use in current pregnancy
6. History of sickle cell anemia, sickle cell trait or other inherited anemia with risk of iron overload
7. Contraindications to MRI (such as claustrophobia, metallic implant, etc.) based on MRI Screening

8. Participation in other interventional clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial
9. Any physical or psychological symptom, based on the clinical judgment of the study physician that would make a participant unsuitable for the study.

Final subject eligibility will be determined by the Principal Investigator or Sub-Investigator delegated the corresponding task.

SUBJECT IDENTIFICATION AND RECRUITMENT

Identification in clinical practice: Investigators own practice

Subjects will be identified at the Center for Perinatal Care ultrasound diagnosis unit. We will approach all subjects with diagnosis of FGR between 27 0/7 - 32 6/7 weeks gestation. All subjects with diagnosis of FGR will be approached only once at the time of ultrasound diagnosis visit at the CPC located at UnityPoint Health-Meriter. It will be recorded in the US reporting system using internal messaging once a subject has been approached and has declined participation. Once the patient has been diagnosed with FGR, the fetal care coordinator or other physicians in the CPC, will tell the patient about an option for participating in a research study, if the pt. is interested Dr. Antony will explain the study. The research coordinator will explain the study further and be responsible for consenting the patient.

We anticipate recruiting 20 total subjects, however, we request permission to approach 60 subjects to achieve full recruitment. The subjects with FGR are far more motivated to undergo additional imaging that may provide insight into why they may have or actually have FGR. Therefore our ratio of recruited to approached is 1 to 3.

Identification in clinical practice: other

UnityPoint Health-Meriter Hospital is the primary facility for the UW obstetricians, several non-UW obstetric groups, several family physicians and UW midwifery group. The patients are seen at several sites within the area, which include UW Medical Foundation (UWMF) and UW Hospital and Clinics outpatient facilities, UWMF Family Medicine clinics and UW clinical teaching faculty outpatient clinics and MFM clinic. All the obstetrical providers participate in either the UW department meeting or the Meriter OB/GYN Department meetings. Thus, we have a very effective direct access to all the clinical providers and use department meeting forums to inform them about this project.

We, with their permissions, communicate with all the outpatient clinical sites' staff about this study. Patients are introduced to the research opportunity by someone involved in their clinical care. Clinic staff and physicians simply inform potential subjects of this study and advise them if they are interested to either contact the study coordinator or complete the, "permission to contact" for allowing the research coordinator to contact them directly to provide more specific information and for scheduling a screening visit.

Medical record identification

Subjects may be identified before being approached by examining the weekly clinical ultrasound schedule for patients who may fit the eligibility criteria. Study team members who have authorized access to electronic medical records may preview the provider schedules and do gross eligibility screening prior to the subjects being approached.

If a potential subject is identified, a member of the clinical care team will be notified by research personnel to approach the patient to determine if the potential subject is interested in participating in the study. In order to identify potential study participants, medical records will be reviewed prior to consenting.

SUBJECT REMUNERATION AND COSTS

The subject will be paid $200 for completing the ferumoxtyol infusion and the MRI at Study Visit 1 and $100 for completing the MRI at Study Visit 2. The maximum amount of money a subject may receive is $300.

EARLY TERMINATION AND WITHDRAWAL

Subjects are free to withdraw from participation in the study at any time upon request.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- Subject non-compliance with study requirements (e.g., study intervention non-compliance)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation
- There is evidence of progressive disease or unacceptable toxicity
- If a subject does not complete either visit within the visit window, then she will be withdrawn from study treatment. A subject will also be withdrawn from study treatment if she develops any of the exclusionary criteria during the study.

Subjects who sign the informed consent form but do not receive the study intervention will be replaced. Subjects who sign the informed consent form and receive the study intervention, then subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

The following actions must be taken if a subject withdraws, or fails to return for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject. These contact attempts shall be documented in the study file.
- If the subject continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

The study team will attempt to obtain the following information from subjects following early termination or withdrawal: reason for withdrawal.

Replacement of Subjects
Up to 2 subjects may be replaced if they do not complete either the infusion or MRI at Visit 1.

To minimize loss to follow-up and missing data, the study coordinator will remind the subjects of all upcoming appointments or study tasks. Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject. These contact attempts shall be documented in the study file. The coordinator will check the subject's medical record for the most up to date contact information.

FERUMOXTYOL INTERVENTION

Ferumoxtyol
Feraheme® (ferumoxytol) infusion is an iron replacement product currently FDA approved for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have chronic kidney disease (CKD). To the best of our knowledge ferumoxytol is the only intravenous iron preparation that was used to localize macrophages at the site of homing in human beings. Ferumoxytol has also been investigated as an alternative in magnetic resonance angiography (MRA) for individuals who are allergic to conventional contrast agents.

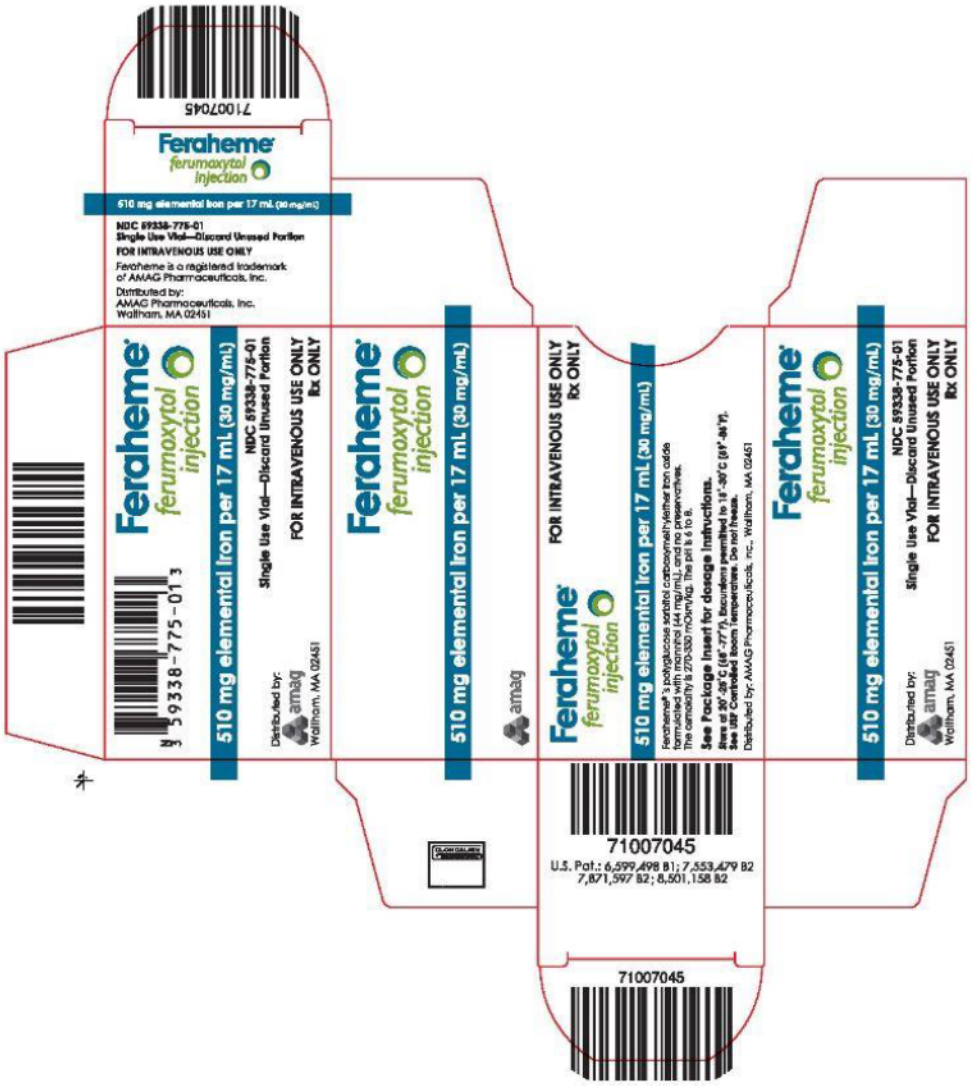
Source
All study drug will be provided free of charge by AMAG Pharmaceuticals, Inc during the treatment phase.

AMAG Pharmaceuticals, Inc will distribute investigational product to the study sites. Each shipment will include a packing slip. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Manual of Procedures. The contents of the shipment will then be reviewed and verified against the packing slip, and will be documented as instructed at the initiation visit.

Each site's investigational pharmacy will be responsible for procuring Feraheme.

Packaging and Labeling
See package display label below.

AMAG > will provide <17 ml in 1 vial, labeled with information on warnings, handling and storage.]



Preparation
The investigational drug pharmacy at UPH-Meriter Hospital will prepare IV solution as follows:
Check product for tampering and/or exposure to high temperatures.
Open bottle using standard protocols for handling biohazardous material.
For this study, we will dilute half of the recommended initial dose, i.e. 255 mg in 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. We will give Feraheme only once, in one infusion of 255 mg to each subject who has consented for this study.

Storage and Stability

Investigational product will be stored separately from normal hospital stocks and will be stored in a securely locked area accessible only to authorized trial personnel until dispensed. The temperature will be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, the investigational product must not be administered, and the site investigator or responsible person should contact AMAG Pharmaceuticals, Inc for further instructions.

Feraheme should be stored at 20° to 25°C (68° to 77°F). Excursions permitted to 15° – 30°C (59° – 86°F). Reconstituted Feraheme should be used immediately but may be stored at controlled room temperature (25° ± 2°C) for up to 4 hours, or refrigerated (2°-8°C) for up to 48 hours.

Accountability
The study monitoring plan assures that quality review activities related to study drug receipt, storage, dispensing, tracking, and destruction are performed to ensure consistent administration of the investigational product.

The person in charge of product management at the site will maintain records of product delivery, site inventory, and product disposal or return. The research program manager will verify product accountability records against the record of administered doses in the electronic case report forms (eCRFs) and the source documents.

In case of any expected or potential shortage of product during the trial, the investigator or an authorized designee should alert the research program manager as soon as possible, so that a shipment can be arranged. In the event of a quality issue, the site should quarantine the investigational product and contact the company, AMAG Pharmaceuticals, Inc, for further instructions.

Dosing and Administration

The UPH-Meriter pharmacy does standard weight-based dosing, based on the UW Health guidelines. The recommended dose of Feraheme is an initial 510 mg dose

followed by a second 510 mg dose 3 to 8 days later. For this study, we will dilute half of the recommended initial dose, i.e. 255 mg in 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. We will give Feraheme only once, in one infusion of 255 mg to each subject who has consented for this study.

Patients will receive an infusion of ferumoxytol and a same day MRI within 1-2 weeks of FGR diagnosis. This visit could occur anytime between 28 0/7 - 34 6/7 weeks gestation.

All subjects will arrive at UnityPoint Health-Meriter Hospital obstetric triage unit as prescheduled for ferumoxytol infusion. In the triage unit, the nurse will obtain baseline vital signs, including maternal pulse, blood pressure, and fetal heart rate. Following this, the nurse will initiate an infusion dose of ferumoxytol (dose). The patients will be monitored at 5 to 15-minute intervals, for pulse, blood pressure, respiration, and fetal heart rate, along with an adverse event review. In an adverse effect occurs, the attending physician, anesthesiologist and triage staff would be notified. This event will be handled similarly to any other medical emergency in triage. This infusion will last 30 minutes followed by 30 minutes of monitoring. However, the overall study visit is anticipated to last 1-2 hours this is to allow enough time for the patient to check in to triage and get settled before initiating the ferumoxytol infusion.

Following the ferumoxytol infusion, the patient will receive the first 60-minute MRI at the UW Hospital, WIMR or 1 S. Park location within 1-15 hours after completion of the ferumoxytol infusion. The purpose of this MRI is for the detection of intervillous placenta blood, placental lesions and detection of macrophages at implantation site:

Supportive Care

If there is an unforeseen adverse reaction, we would use the usual and customary treatment for iron infusion-associated allergic reactions, which would be no different from response to any other allergic reaction case at the obstetric triage unit. In order to facilitate and create the utmost safety, we would pre-notify the obstetric anesthesiologist on the unit in advance of the scheduled procedure. After the patient completes intravenous iron infusion and has been monitored for at least a total of an hour and has not experienced any adverse side effects, the patient will be advised to present herself for the ferumoxytol-MRI. The coordination for this will be provided by the study coordinator assigned to the study.

The vast majority of serious allergic reactions occur within short time (10 minutes) of starting the infusion. No reactions have been reported after 30 minutes of infusion. We have arbitrarily extended observation period to one hour and no one is expected to develop allergic reactions after that time.

Patients have hemogram done routinely for clinical care at 28 weeks. We will perform a panel of iron study (serum iron and transferrin levels) two-three weeks after the day of infusion. TIBC is not useful in settings of patients having received iron infusion, hence is not included in the panel.

Concomitant Therapy
There are no prohibited concomitant medications, therapies or supplements.

STUDY VISITS AND PROCEDURES
The procedures performed at each study visit are listed in the table below.

Procedure	Screening	Visit 1	Visit 2	Visit 3	Delivery	End of Study/ Postpartum
Visit Window	**28 0/7 – 34 6/7 wk GA**	**29 0/7 - 35 6/7 wk GA**	**29 3/7 - 36 4/7 wk GA**	**2-3 wk after ferumoxytol**		**Delivery + 6 wks**
Informed Consent	X					
Review Eligibility Criteria	X					
Demographics	X					
Review Concomitant Medications	X	X	X		X	X
Medical History	X				X	
Vital Signs		X	X			
Ferumoxytol Administration		X				
MRI		X	X			
Biological specimen collection	X				X	
Adverse Events Review/ Assessment		X	X	X	X	X
Iron Panel				X		

Screening and Enrollment

Informed Consent
Patients who express interest in the study will be referred to study personnel, who will discuss the protocol, including all procedures that will be administered as part of this research, the risks associated with participation, and the timeline for all research visits. Any questions concerning study participation will be answered before written consent is

obtained. Potential subjects will be encouraged to take as much time as needed to consider participation.

An informed consent for participation in the study is obtained from each eligible patient, including a consent for Fe-MRI. Patients of all ethnicities for both groups are eligible.

Screening for Eligibility

1. A subject would fill out a permission to contact form in their respective clinic and the research coordinator would call the patient.
2. The telephone script would be used to determine baseline eligibility. The coordinator may send the subject a consent form so they have time to review before the consenting visit. The phone script will also ask patients if they would allow the coordinator to review their medical records before scheduling a consenting visit.
3. A consenting visit would be set up at the Center for Perinatal Care so that the subject could meet with the coordinator to ask questions and sign the informed consent document.
4. The inclusion/exclusion criteria will be reviewed with the patient.
5. Once the patient has signed the consent form documents, she will be given a copy for her records.
6. The sensitive information will be collected by the review of medical records. General information that we can rely on the patient will be collected by oral interview, however rigorous review of medical records would be necessary before enrolling the subject into the study. Per protocol, Exclusion criteria: if a patient is using tobacco/alcohol/drugs they would be excluded from the study since these factors could alter the outcome of their pregnancy putting these patients at higher risk. A MRI screening compatibility form will be completed to make sure it is safe for the patient to have an MRI performed. This is a standard form used by UW for all imaging procedures.

Enrollment

A research subject will be defined as “enrolled” in the study when they meet the following criteria:

- The subject has been consented by study staff.
- The subject and study staff have completed all screening documentation.
- The PI has verified that the subject meets all of the inclusion criteria.
- The PI has verified that subject meets none of the exclusion criteria.
- The subject has been assigned to the protocol by study staff.
- The subject has scheduled a study visit.
- The subject has received the study intervention.

On Study/Follow-up Visits

All procedures are described in detail in the “Research Procedure Descriptions” section of the protocol.

After subjects have been enrolled, the On-Study/Follow-up visit and the procedures performed at each visit are described in detail below.

Visit 1Ferumoxytol Infusion and 1st MRI
All procedures at this visit are for research purposes only. The infusion process, including setup of infusion and subject in the triage, subject monitoring and post-infusion monitoring will be performed as part of a paid service by qualified staff at UPH-Meriter Hospital triage. The MRI will be performed by qualified and trained clinical staff as part of a paid service at the locations listed below. The study coordinator will be present during all procedures.

Patients will receive an infusion of ferumoxytol and a same day MRI within 1-2 weeks of FGR diagnosis. This visit could occur anytime between 29 0/7 - 35 6/7 weeks gestation.

All subjects will arrive at UnityPoint Health-Meriter Hospital obstetric triage unit as prescheduled for ferumoxytol infusion. In the triage unit, the nurse will obtain baseline vital signs, including maternal pulse, blood pressure, and fetal heart rate. Following this, the nurse will initiate an infusion dose of ferumoxytol (dose). The patients will be monitored at 5 to 15-minute intervals, for pulse, blood pressure, respiration, and fetal heart rate, along with an adverse event review. In an adverse effect occurs, the attending physician, anesthesiologist and triage staff would be notified. This event will be handled similarly to any other medical emergency in triage. This infusion will last 30 minutes followed by 30 minutes of monitoring. However, the overall study visit is anticipated to last 1-2 hours this is to allow enough time for the patient to check in to triage and get settled before initiating the ferumoxytol infusion.

Following the ferumoxytol infusion, the patient will receive the first 60-minute MRI at the UW Hospital, WIMR or 1 S. Park location within 1-15 hours after completion of the ferumoxytol infusion. The purpose of this MRI is for the detection of intervillous placenta blood, placental lesions and detection of macrophages at implantation site:

Visit #2: 2nd MRI
All procedures at this visit are for research purposes only. The MRI will be performed by qualified and trained clinical staff as part of a paid service at the locations listed below. The study coordinator will be present during all procedures.

The second visit and MRI will occur 3-5 days after visit 1. This visit could occur anytime between 29 3/7 - 36 4/7 weeks gestation at the locations listed above. The purpose of the second MRI to detect implantation sites for macrophages after ferumoxytol is cleared from the body. This procedure will only last 60 minutes.

The study coordinator will perform all the following procedures:

- All FGR diagnosis data will be reviewed and collected.
- Subjects will be scheduled for a 60-minute MRI and adverse event review.
- A medical record review will follow the subject's regularly scheduled visit.

Visit #3: Iron Panel (Blood draw)

We will perform a panel of iron study (serum iron and transferrin levels) two-three weeks after the day of infusion. This visit will occur at any time between 2-3 weeks after the ferumoxytol infusion. Every effort will be made to have this visit coincide with a standard of care visit, but in the event this cannot happen within window, a research only visit will be created.

- Blood collection will be performed by phlebotomy staff at UPH-Meriter Hospital, blood sample will be sent to Meriter Labs for analysis.
- Results will be uploaded to the subject's medical record.

Delivery Visit (time of delivery)
The procedures performed for research purposes only include:

- Blood/urine collection, will be performed as a paid service by nursing or phlebotomy staff at UPH-Meriter Hospital. This procedure should last only five minutes.
- maternal and newborn medical record review, will be performed by the study coordinator
- The findings from the placenta pathology report will be used to correlate with MRI findings. There will be no placental collection. The study coordinator will review the pathology report from the subject's medical record.

The standard of care procedures will include delivery of the baby and all associated procedures, performed by clinical staff.

Postpartum Follow-up
This follow-up is for research purposes only and will be performed by the study coordinator. The phone call should not last more than 15 minutes.

- Follow-up Phone Call (any time post-delivery, up to 6 weeks postpartum)
- Adverse event review with subject.
- Review of Concomitant medication

STATISTICAL CONSIDERATIONS

This is an exploratory investigation of placental lesions identification by MRI and there is not data available to provide sample size justification. The goal of this sub-project is to expand the scope of our project to asses human placenta function in on-going pregnancies. Expanding the project to include women with diagnosis of FGR as per our discussion with NICHD program officer and NICHD-HPP scientific leadership was granted to us and will allow us to develop robust preliminary data for future NIH grant application. Our plan is to conduct MRI imaging and correlate the findings with placental pathology findings. We request permission to approach 60 subjects and anticipate to study a total of 20 subjects: this will provide adequate data to define future direction of this research.

RISKS AND BENEFITS

Potential direct benefits to subjects.
Results from the MRI scans will be uploaded to the subjects' EMRs. The study PI will also share the results with the subject's primary obstetric physician and will provide appropriate counseling to the subject. The clinical investigator, Dr. Antony is a Maternal-Fetal Medicine (MFM) specialist who can explain the findings of the MRI imaging and may help to reduce the subjects' anxiety. A recommendation to increase clinical monitoring may be made by the study PI based on MRI findings.

The PI will personally discuss imaging results with the clinician who is providing direct care to subject in question. The subject's primary care clinician will be involved in the discussion with subjects regarding study MRI results and any additional recommended follow-up (e.g., added subject/fetal growth monitoring). However, it will be the provider's decision if they want to take the findings of the study into consideration to make any modifications in the patient's clinical care and monitoring.

The current standard of care for FGR cases consist of increased monitoring in the following manner: non-stress test (NST) performed 2 times per week, Doppler velocimetry performed 1 time per week, and growth ultrasound performed 1 time per month after the diagnosis of FGR until delivery. Depending on the clinical manifestations, the clinicians may decrease or increase monitoring frequency for the ultimate goal of preventing perinatal mortality and morbidity. Fetal monitoring frequency will not be increased solely based on findings from the study, but rather taking into consideration other factors regarding maternal and fetal health.

MFM clinicians use multiple tests to determine the course of care in high-risk pregnancies. The use of study results from MRI findings would only confirm standard of care decisions and not directly influence clinical care. It is not unreasonable to connect investigational imaging method knowledge to pre-existing knowledge.

The only current method to detect placental lesions is through pathologic examination of the placenta after delivery. It has been well documented that FGR fetuses with confirmed placental lesions have worse post-natal outcomes than those whose placental lesions are not confirmed. The purpose of the proposed study is to detect placental lesions before the fetus is born in an effort to come up with a better treatment plan to improve neonatal outcomes. The MRI has the potential to indicate which fetuses, based on presence or absence of placental lesions, will have a better or worse outcome at delivery. The MRI would be one of many tests taken into consideration when determining best clinical management of patients with FGR diagnosis.

The following benefits are anticipated.
1. Potential to confirm that there are no perfusion defects and no evidence of macrophage recruitment in the placental bed. This would be enormously reassuring to the subjects, particularly the absence of perfusion defects.

2. If perfusion defects or recruitment of macrophages in the placental bed are detected, we would recommend the following modifications to their clinical care.
a. If fetal growth is not already being monitored, we would recommend to the clinic that additional monitoring be added to clinical care.
b. The number of visits for patients would be increased to monitor for development of new or acceleration of hypertension, indicative of pre-eclampsia.
c. Depending on the severity of placental lesions, we may inform to clinicians to which patients may require earlier delivery.

In this context, these three modifications will empower clinicians to provide individualized care based on novel advanced and sophisticated imaging information.

The benefits of the ferumoxytol intervention are predominantly for the mother and ancillary benefits to the fetus may accrue. Ferumoxytol will be used as a contrast agent for research and subjects would personally benefit from this intervention. Study use of ferumoxtyol involves the potential for minimal risk to subjects and fetus/pregnancy but the risk cannot be stated categorically simply because such data does not exist in published literature. However, we suggest that ferumoxtyol is likely to emerge as the safest iron contrast agent for assessment of pregnancy and other complications during pregnancy and treatment of anemia.

We may identify placental lesions in FGR cases that may be a potential benefit of participation in this study for FGR patients. If we identify homing of macrophages, again this information has potential benefit for patients to know what underlying process may be. We will commit to provide the findings regarding placental lesions and macrophages to the subject and their primary obstetric care physician during the on-going pregnancy in the event that the information may be useful to understand the potential underlying cause of FGR. Full disclosure will be made that this is not yet a diagnostic tool.

Subject enrollment is limited to those subjects with FGR because a demonstrable potential benefit to the subjects without FGR cannot be based on our conceptual framework of our entire human placental project. This was intended to weigh the equation in favor of potential benefit.

Potential benefits of this research to society.
This research will advance the knowledge and technical expertise for detection of placental lesions in an on-going pregnancy. It will also advance knowledge and technical expertise for detection of homing of inflammatory cell in the placental bed. Future research will be possible armed with results of this work which may be paradigm shifting in care and management of cases of FGR and preeclampsia.

Potential Risks
Clinical treatment of patient diagnosed with FGR:
All subjects diagnosed with FGR are monitored closely and are asked to return for a fetal growth ultrasound every 4 weeks as per routine clinical practice once a diagnosis is made. These fetal growth scans is standard of care for all subjects with FGR

diagnosis. All FGR patients will continue to receive weekly Doppler assessment of umbilical arteries and middle cerebral artery and amniotic fluid assessment. In addition, these patients also undergo clinically indicated fetal heart rate monitoring (non-stress test) twice a week.

MRI

The earliest time in gestation we are performing MRI is at 28 weeks and MRI methods are generally considered safe when applied after completion of the first trimester. It is also common clinical practice to repeat MRI. As far as the American College of Radiologists is concerned, first-trimester MR imaging may be performed then (as well as in any other trimester), as long as the risks/benefits ratios are in favor of performing such a study. This is primarily based on the consideration that the modern MR machines are capable of continuously measuring the RF and have a set threshold at which they shut off if RF exceeds the set limits, so MRIs are safe in terms of potential tissue heat generation and cellular damage. We perform two MRI studies for the purpose of blood flow measurements and perfusion assessment. We already commonly perform two and occasionally three MR imaging sessions to image fetuses and to obtain clinical data whenever there is a concern about the fetus and/or in cases with placenta previa and/or concern about placenta accreta, and those sessions are as long as we are proposing for this research.

All our research MRI equipment is the most advanced and modern equipment with RF safety built-in. For obese subjects, we have wide bore research MRI equipment allowing the most comfortable positions, including left lateral positions. All the patients are provided with an ability to ring the buzzer and stop the MRI procedure if either they have claustrophobia and/or they are uncomfortable in the position. The left lateral positions become relevant and we can position our subjects into left lateral positions as such.

Study Drug

We are not proposing a new route of administration for this approved drug. However, we are proposing to use this drug in pregnant women. Pregnant women are at risk for developing clinical complications of pregnancy including preeclampsia and fetal growth restriction. These complications are unique to pregnant women. There have been limited investigations on pregnant women to advance the science leading to development of technologies that may help identify women who may develop these complications, before they clinically manifest these complications.

Once there are clinical manifestations of these complications, there is nothing that can be done to prevent these complications and currently options for treatment are non-existent except temporization to provide limited benefit to developing baby at significant risks to the mother by postponing delivery. Hence, it is essential and critical that we conduct such studies in pregnant women to advance this science and develop advanced tests of placenta function with high degree of precision to help mothers and their babies in the future.

Limited available data with ferumoxytol use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with untreated IDA in pregnancy, which far exceeds the risks and benefits of Ferumoxytol infusion during pregnancy. In animal studies, administration of ferumoxytol to pregnant rabbits during organogenesis caused adverse developmental outcomes including fetal malformations and decreased fetal weights at maternally toxic doses of 6 times the estimated human daily dose.

Impact on the Fetus
Regarding the impact of the agent on the fetus, the physiology of colloid iron supports the statement that ferumoxytol does not cross the placenta and enter the fetal circulation. All iron is absorbed in the macrophages in the maternal immune system. Ferumoxtyol does not cross the placenta as all iron is cleared by the mother. It was determined that this iron does not go into the fetal circulation, as it is a colloidal superparamagnetic iron carbohydrate complex that is trapped in the maternal immune system.

Our IND application fully describes the iron metabolism, ferumoxtyol safety and iron delivery to the fetus. (see section 9. Nonclinical Toxicology). In addition, as stated in the summary of our use of ferumoxytol as a MRI contrast agent in rhesus macaques in our IND application, there was “not significant ferumoxtyol being transported across the placenta and into the fetus.” (see page 8 of the IND application, “Ferumoxytol Detection Following Infusion in Rhesus Macaque Pregnancy.”

All pregnant women are anemic, so there is no risk for iron overload. Long-lasting buildup is not possible, as all iron will be cleared by maternal macrophages within a few days. We describe the study of ferumoxytol use in pregnancy in our IND application and the determination of our colleagues that ferumoxytol is cleared from the blood 24 hours post-infusion. We will only be administering a single infusion in the proposed study. We will be only selecting subjects who are not at risk for iron overload and will be monitoring their iron status. We are also only using half the recommended dose that is used to treat anemia in pregnant women.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Most birth defects occur during the period of embryogenesis (organogenesis), which is completed in humans at 14 weeks gestation, based on menstrual history. We plan to use ferumoxytol during the 24-28 week window, which is well beyond the period of organogenesis; hence use of ferumoxytol at indicated time is unlikely to cause birth defects in study participants. Subjects with fetal birth defects diagnosed during the first trimester or at 20 weeks are excluded from the study.

Disease-associated maternal and/or embryo/fetal risk: Untreated IDA in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse

pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

Preeclampsia and FGR Risks
Patient with preeclampsia and /or fetal growth restriction are at increased risk of preterm delivery, cerebral palsy and fetal/neonatal death. There are many perinatal implications of preterm delivery including common complications like respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis and bronchopulmonary dysplasia with long-term need for oxygen.

Allergic/anaphylactic reaction
Regarding the possibility of an allergic/anaphylactic reaction and its impact on the pregnancy and fetus, the impact would not be severe, based on data on allergic reaction from AMAG Corporation, University of Arizona and Georgetown University School of Medicine, described below. Ferumoxtyol has been used clinically in pregnant women at Meriter.

All intravenous iron infusions have some serious risks including anaphylactic reactions and death. However, critical review of the literature shows that these events are rare and some of the events are due to physician interventions for treatment of minor allergic reactions. These events most frequently have been reported in older patients and individuals with underlying chronic conditions. We wish to emphasize that Ferumoxytol is one of the iron preparation with lowest rate of reactions. It is approved for use during pregnancy. We have provided extensive details in our IND application based on which we now have FDA approval to conduct this research as proposed.

All intravenous iron preparations have been described to have serious allergic reactions in a small number of subjects receiving such treatments. These serious adverse events for ferumoxytol include anaphylactic reactions. The agency is now requiring a boxed warning with new cautions and has asked AMAG Pharmaceuticals to add a new contraindication of a strong recommendation against use in patients who have had an allergic reaction to any intravenous (IV) iron-replacement product.

Critical analysis of literature suggests that anaphylaxis may occur in 0.02 % of subjects receiving ferumoxytol, making it one of the safest intravenous iron preparation. Furthermore, the data on SAEs derived from Adverse Event Reporting System have inherent limitations of limited information on safety precautions taken prior to iron infusion and treatments rendered for suspected adverse events, since some of the treatments used for drug reactions to intravenous iron themselves have inherent risks of causing serious adverse events compounding the interpretation of these data.

Other common adverse reactions reported in Ferumoxytol-treated patients include diarrhea (4.0%), constipation (2.1%) and hypertension (1.0%).

Toxicological data in animals or prior studies in humans with ferumoxytol does not suggest additional risks of particular severity or seriousness over and above what is

described above. This is so because we plan to use substantially lower dose during gestational window well beyond the period of organogenesis.

If there is an unforeseen adverse reaction, we would use the usual and customary treatment for iron infusion-associated allergic reactions, which would be no different from response to any other allergic reaction case at the obstetric triage unit. In order to facilitate and create the utmost safety, we would pre-notify the obstetric anesthesiologist on the unit in advance of the scheduled procedure. After the patient completes intravenous iron infusion and has been monitored for at least a total of an hour and has not experienced any adverse side effects, the patient will be advised to present herself for the ferumoxytol-MRI. The coordination for this will be provided by the study coordinator assigned to the study.

The vast majority of serious allergic reactions occur within short time (10 minutes) of starting the infusion. No reactions have been reported after 30 minutes of infusion. We have arbitrarily extended observation period to one hour and no one is expected to develop allergic reactions after that time.

Patients have hemogram done routinely for clinical care at 28 weeks. We will perform a panel of iron study (serum iron and transferrin levels) two-three weeks after the day of infusion. TIBC is not useful in settings of patients having received iron infusion, hence is not included in the panel.

Supporting Documentation for Safety of Ferumoxyol use in Pregnant Women

Ferumoxytol - Pregnancy reports in AMAG safety database
A search of the AMAG safety database was performed to obtain information regarding pregnancy in patients treated with ferumoxytol. The search retrieved 15 total case reports, five were reported from spontaneous sources and 10 reports were from sponsored clinical trials. Four (4) of the subjects in the sponsored clinical trials were determined to be pregnant at screening and thus never received the study drug. After exclusion of these case reports, there were a total number of 11 subjects with exposure to ferumoxytol before (six subjects) or after (three subjects) conception (in two subjects exposure details were not provided). Of these case reports, 5 were received from spontaneous sources and six were received from sponsored clinical trials. One subject was enrolled in AMAG-FER-CKD-401, two subjects were enrolled in AMAG-FER-IDA-301 and three subjects were enrolled in AMAG-FER-IDA-303 (extension study). Summary of pregnancy cases is provided below.

There was no pregnancy outcome data provided in four of the cases. The remaining cases reported no complications during labor and delivery. In addition, the neonates had no congenital anomalies or medical problems.

In one case, a 37-year-old subject reported premature delivery at 25 weeks of gestation with stillbirth several months following study completion. Considering that inception occurred months after study drug (ferumoxytol) discontinuation, as well as the subject's

multiple comorbidities and risk factors such age, gravida 3/para 1,etc, it suggested that these AEs most likely arose spontaneously and are unconnected to the study drug.

Base on the review of these cases, there is no indication of negative impact on fetal development or pregnancy outcome after pre conception and post conception exposure to ferumoxytol.

Ferumoxytol – Pregnancy: Michael Auerbach, Georgetown University School of Medicine
Dr. Auerbach is a clinical professor in Hematology and Oncology at the Georgetown University School of Medicine. A letter of support from Dr. Auerbach is attached to the IRB application in supplemental documents.

Based on Dr. Auerbach's extensive clinical experience with ferumoxytol, including at least 140 patients who were pregnant, there were no serious adverse events and no reports of negative outcomes at delivery; with all patients responding adequately by improving their hematocrit.

Ferumoxytol – Pregnancy; Meghan Hill, University of Arizona College of Medicine-Tucson
This study at the University of Arizona (UA) (PI: Hill) is recruiting women with anemia in pregnancy greater than 20 weeks gestation for treatment with either oral iron or with feraheme. They are randomized in a 1:1 allocation. So far, 23 women have been recruited, 11 in the oral iron arm and 12 in the IV feraheme arm.

There have been no anaphylactic reactions and no concerns raised otherwise about the study. The study is too early in recruitment to determine outcomes such as a change in laboratory values or birth outcomes, but there has not been a concerning pattern emerging in any outcomes at this early stage.

Prior administration of Ferumoxytol at UPH-Meriter Hospital
The protocol at Unity Point Meriter was developed based on our research proposal and dose for clinical contrast-MRI at Meriter is same as in our research protocol. The following were the results from women administered ferumoxtyol during pregnancy. UPH-Meriter was unable to provide us with pregnancy outcome data. Ferumoxytol is used as a contrast agent for pulmonary angiography in pregnancy patients who present with symptoms of pulmonary embolism. It is used during pregnancy for assessment of pulmonary vasculature.

The protocol was established in late 2017. All ferumoxytol is ordered by the ordering providers, administered on their respective floors, and monitored by their staff. The UPH-Meriter pharmacists have created guidelines regarding dosing, including reporting adverse reactions.

The UPH-Meriter pharmacy does standard weight-based dosing, based on the UW Health guidelines. The standard dose is 3 mg/kg with a maximum of 510 mg.

A search was done of UPH-Meriter pharmacy records for all administration of ferumoxytol for the past 15 months, between 12/04/2017 and 4/01/2019. This medication was administered 29 times to 27 pregnant patients and 2 non-pregnant patients. The two non-pregnant patients were men, who acute kidney injury.

Ultimately, PE was ruled out in all the women. Two patients required another imaging study (CTA in both cases) to provide further information. One patient ruled out for PE, but was found to have cholelithiasis.

One patient developed what appears to be an anaphylactoid reaction within about 5 minutes of the start of the infusion. The infusion was stopped and the patient was placed on oxygen and symptoms stopped as well. Patient had a different imaging procedure. In the case of the woman infused during pregnancy at UnityPoint Health-Meriter that we reported in IRB # 2015-1222, we are not able to access the medical records of this patient for research purposes and report results from a medical record, unless that person is part of a research study.

However, as a physician in the Maternal-Fetal Medicine (MFM) division, the PI is familiar with clinical events related to ferumoxytol infusion for any pregnant women. It was not known whether the patient truly had an anaphylactic reaction resulting from the ferumoxytol infusion. After clinical evaluation, it was determined that symptoms were ascribed to pre-existing clinical status. Her pregnancy outcome was normal.

Sample collection
Risks associated with blood sample collection is limited to minor bruising, slight pain, and, in very rare instances, syncope. Collection of urine samples results in a minor inconvenience for subjects enrolled.

<u>Adventitious findings</u>
We are mindful of small possibility that we may detect some clinically significant findings in the mother or the fetus.

If a clinically significant finding is seen on any of the MRI imaging used for this research, we will have such findings reviewed by the appropriate specialists (MRI research team, Dr. Antony, and Dr. Shah) to confirm the significance. In the event that it is in the best interest of the subject to be made aware of the findings, we will communicate our findings to the subject's primary Ob care physician and the subject. Dr. Antony will personally communicate with the subject's provider, but it will be the provider's decision to consider these study findings to decide if modifications in the subject's clinical care and monitoring are warranted. All other incidental findings will be recorded in our database but not revealed or discussed with the subjects, unless it is important for the subject's medical care.

Regarding the ferumoxytol infusion and following MRI, MRI interpretation will be provided by the MRI research team, headed by Dr. Wieben, PhD, Dr. Reeder, MD-PhD,

Dr. Hernandez, PhD, Dr. Antony and Dr. Shah. The MRI research team will analyze and interpret the findings of the MRI imaging to determine if macrophages are detected in the uterine wall. The study PI, Dr. Shah, and Dr. Antony will make the final decision for interpretation of the MRI imaging.

The PI will provide appropriate counseling to the subject and their primary obstetrician, as he is a Maternal-Fetal Medicine (MFM) specialist who can explain the findings and to reduce the subjects' anxiety. Dr. Antony is a UW Ob/Gyn physician, working in the UPH-Meriter Perinatal Clinic who routinely reviews MRI scans and counsels patients with at-risk pregnancies. Dr. Antony is the most qualified physician-scientist in the region to explain to the subject the meaning of the findings and how she will be monitored.

The study PI will disclose results from the MRI scan to subjects. The primary finding will be the presence or absence of macrophages at the maternal-fetal interface at the site of implantation. If we observe other changes in the placenta, such as lack of perfusion in intervillous space, we will also report this finding. The PI will discuss these findings with the subject in layman's terms and describe the modifications in clinical care as a result of these findings.

Interpretation of clinical monitoring will be enhanced based on MRI findings.

We may confirm that there are no perfusion defects and no evidence of macrophage recruitment in the placental bed. This would be enormously reassuring to the subjects, particularly the absence of perfusion defects. However we will not suggest to the clinician to change the course of monitoring.

If we detect perfusion defects or recruitment of macrophages in the placental bed, we would suggest that these subjects have following modification in clinical care.
a. If fetal growth is not already being monitored, we would recommend to the clinic that additional monitoring be added to clinical care.
b. The number of visits for patients may be increased to monitor for development of new or acceleration of hypertension, indicative of pre-eclampsia.
c. Depending on the severity of placental lesions, we may inform clinicians as to which patients may require earlier delivery.

In this context, these three modifications will empower clinicians to provide individualized care based on novel advanced and sophisticated imaging information.

Review of MRI by the MRI research team will occur within one week and an appointment for counseling for the subject would be scheduled within the following week. This timeline of counseling the subject within 2 weeks is safe given that a) the subject is already being monitored for the emergence of disease diagnosis and, b) we are detecting placental lesions that are premonition of emergence of severe fetal growth restriction or preeclampsia, which are not likely to occur until 4-8 weeks after the infusion MRI.

The PI, a physician at the Center for Perinatal Care clinic, will have a face to face research visit with the subject about their MRI findings. PI will also contact with the subject's physician to discuss the results. This will occur within two weeks of the last MRI scan.

Results from the MRIs will be made available in the subject's medical record.

Blood and urine samples collected for analysis will not provide clinical information, this is pioneering work and no clinical data exists for this kind of work.

DATA COLLECTION, HANDLING, AND RECORD KEEPING

Privacy/Confidentiality

The paper research records will be kept confidential. The results of this study may also be used for medical and scientific publications, but the subject will not be identified personally in any presentations or reports related to this research.

The information collected from subjects and from their medical records will be used by the researchers and research staff of the UW-Madison and its affiliates (the University of Wisconsin Hospital and Clinics and the University of Wisconsin Medical Foundation) for this study. It may also be shared with others at the UW-Madison.

Any paper documentation including the consent form will be kept in the UW Ob/Gyn clinical research office (located at McConnell Hall) and locked in a cabinet. The consent form will be stored in a separate file cabinet from the patient data. There is limited access to the office and only the study coordinators have a key to the locked files. Patient information that is entered into the database stored on department servers will be coded; only the investigators involved in this study will have access to the research-related information. Results from this study may also be used for medical and scientific publications, but the subject will not be identified personally in any presentations or reports dealing with this research.

The information will be reported only to the study team, either by Epic note or direct contact. The deidentified data will travel to REDCap so no one other than the study team will have access to the information.

Results from MRI imaging (but not blood or urine test results) will be entered into patient's medical records.

Others at UW-Madison and its affiliates who may need to use the subject's health information in the course of this research:

- UW-Madison regulatory and research oversight boards and offices
- University of Wisconsin financial and accounting services
- Research support services staff at the UW-Madison and its affiliates

Others outside of UW-Madison and its affiliates who may receive the subject's health information, without any identifiable information, in the course of this research:

- National Institutes of Health
- US Food and Drug Administration

Data Collection

Research data collected is coded with a unique study identification number assigned to each subject upon enrollment. Confidentiality is protected by keeping paper research files in a secured office while unsupervised; all excess paper copies will be shredded; data is entered into the secure, password protected clinical trial management software, OnCore and the Research Electronic Data Capture (REDCap) system (refer to the Data Management section for more information); computer monitors have screensavers, login screens will be password protected; workstations are password protected; and firewall security protection is in place.

MRI data will be stored on the UW Department of Radiology PACS (Picture Archiving and Communication System). All workstations used to access and process images are password protected to ensure confidentiality. The MR systems are connected to the network within the hospital firewall, and images and unprocessed image data will be transferred to password-protected computers in the Departments of Radiology and/or Medical Physics.

For all research data sent to PACS, a unique study/subject code is used to identify the imaging data. The unique study number includes the prefix "RMR" allowing it to be identified by a filter on the PACS system as a research scan to be kept separate from any clinical data. This strategy is another measure used to prevent research data from inadvertently being entered into medical records.

Study subjects are asked to provide consent to have left over research samples banked for future unspecified research. Study data as well as specimens are retained for future use. It is not known what these specimens will be used for. Samples and data will be anonymized, with all identifiers removed, including all study codes. The specimens are stored at Meriter hospital in the 7th floor lab of Ian Bird, PhD. This restricted area requires a specified badge for access, only the researchers who work in this lab have access.

- All clinical imaging and biochemical data obtained from this study will be stored. No HIPAA identifiers will be stored.
- U01 Human Placenta Project (HPP) funding under the aegis of NICHD is an organized collaborative effort. Through this mechanism, we may carry out biochemical, genomics and proteomics research but by virtue of our data being de-identified none of the findings can be traced back to a specific participating individual. We do not intend to use these samples for stem cell research or for research activities that may be considered societally unacceptable from human protection perspective.
- Specimens may be used solely by UW researcher collaborating with other U01 HPP centers or with other research institutions.

- Data shared with outside collaborators will be anonymized.
- Data may be stored indefinitely
- Study subjects may not withdraw biosamples once they have been processed.

Data Management

The PI and co-investigators will oversee the management of the study data.
This study will utilize the clinical research management software, Online Collaborative Research Environment (OnCore) and Research Electronic Data Capture (REDCap), both adopted and supported by the School of Medicine and Public Health (SMPH) and available to all researchers conducting clinical research studies. Both instances of the software that will be utilized for this study are supported and managed by the UW Institute for Clinical and Translational Research (ICTR).

Both software systems are sophisticated, web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources such as individual studies and patient registries; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data and Safety Monitoring Boards and biostatisticians.

The ICTR OnCore software provides protocol and subject management functions (e.g. subject scheduling; screening, data organization), maintains updated forms, addresses budget development, billing, and fiscal management, generates summary reports, and provides essential links with other research administration and electronic medical records systems. ICTR OnCore eases the burden of the individual researcher and unifies protocol management within research programs and including researchers at multiple sites, enhancing protocol integrity and regulatory compliance efforts.

The data entered into and managed in the ICTR OnCore system is exported, then imported into ICTR REDCap and combined with MRI and U/S data, allowing the ICTR REDCap system to act as the final data repository. The REDCap data is available to the investigator and statistician(s) for reporting and analysis.

All personnel involved in the study will have undergone requisite human subjects, Good Clinical Practice (GCP) and HIPAA training, in addition to study specific data entry and management training. The MR imaging laboratory will collect, manage and store the study MRI data. The MR imaging laboratory is located within the Departments of Medical Physics and Radiology, both of which are part of the Affiliated Covered Entity (ACE).

Primary Source Documents

The investigators must maintain primary source documents supporting significant data for each subject in the subject's medical notes. These documents, which are considered 'source data', will include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for the subject is being studied

- General information supporting the subject's consent to participate in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of adverse events, and the date study intervention commenced and completed
- Any additional visit during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse experiences
- Original, signed informed consent forms for study participation.

The investigator must also retain all subject specific reports or tests/procedures performed as a requirement of the study (e.g., laboratory results). This documentation, together with the subject's and newborn's hospital/site medical records, is the subject's 'source data' for the study.

Case Report Forms

Case Report Forms (CRFs) will be developed and maintained with the assistance of the ICTR Study Monitoring Services, the ICTR Data Monitoring Committee and the OnCore Support specialist(s) for recording relevant data for each subject. It is the investigator's responsibility to ensure that these are properly, legibly and fully completed and signed where appropriate. The CRFs are used to record study data and are an integral part of the study and subsequent reports.

Data/Record Retention

Records will be retained for a minimum of 7 years after study completion, per UW Madison policy and IRB guidance: https://kb.wisc.edu/sbsedirbs/page.php?id=42378.

FDA Considerations

Ferumoxytol

Principal Investigator has an approved IND application and IRB approval to use ferumoxytol in the main arm of our placenta imaging study. We will apply the same process for this sub-project and have submitted an addendum to our IND to expand the scope of Ferumoxytol use in this sub-project for placental imaging.

MRI

All hardware used to obtain MR images is FDA approved and will be used in accordance with the conditions approved by FDA. The investigational software being used in image acquisition is designed to stay within the current guidelines for MRI safety, established by the FDA. In addition, the investigational software does not meet the definition of a Significant Risk Device as outlined by the FDA under 21 CFR 812.3 as being:

1. Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

2. Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
3. For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The scan protocol will include the following sequences
Localizer scans – FDA approved, clinical sequence

Specific Aim 1: MRI Flow

- 2D Phase Contrast MRI (Flow Imaging) = FDA approved, clinical sequence

Specific Aim 2: MR Perfusion and Oxygenation

- Oxygenation (BOLD MRI) – multi TE gradient echo sequence = FDA approved sequence

Specific Aim 3: MRI Ferumoxytol DCE perfusion data (not investigational sequences) and localization of immune cells.

DATA AND SAFETY MONITORING

Data and Safety Monitoring Plan

We use the UW ICTR Data Monitoring Committee for the purpose of oversight over this study. We have accounted for the fees for the Data Safety Monitoring. The clinical investigator, Dr. Antony, the PI, Dr. Shah and the co-investigator Dr. Wieben, respectively, are responsible for reporting any adverse responses or events that occur. These are reported as per requirement to UW IRB, and to the Data Monitoring Committee. We take advice from the IRB committee and Data Monitoring Committee for appropriate modifications of our procedures in order to avoid such events.

For subjects receiving the ferumoxytol infusion, the PI and study team will monitor any potential impact on the subject and the fetus. The subject will be closely monitored by triage clinical staff during the infusion of ferumoxytol in the triage unit, including the collection of vital signs. With any signs of reactions, the infusion will be stopped. The study coordinator will report any events of this nature, including adverse events and unanticipated problems, to the PI and the DSMB within one business day.

In the weeks following infusion, the PI will discuss the imaging results with the subject and the clinician providing direct care to the subject. Any adverse events will be documented, entered into the subjects study file and reported to the DSMB. After delivery, pregnancy outcome and any potential impact on the fetus will be documented and reviewed with the PI and subject clinician and DSMB. Development of pre-

eclampsia and FGR will not be considered, but will be reported, as an adverse event secondary to ferumoxtyol infusion.

Data Monitoring Committee (DMC)

UW-ICTR has established a Data Monitoring Committee (DMC) to provide a key resource for UW-Madison investigators conducting clinical research. We plan to utilize the UW-ICTR DMC services to ensure appropriate measures are in place to promote subject safety, research integrity and compliance with federal regulations and local policies for individual clinical research protocols. These protocols are deemed in need of DMC review by the PI, the funding agency, the local Scientific Review Committee, or the local IRB, and for which no DMC exists. For these studies, the UW ICTR DMC is the primary data and safety advisory group for the Principal Investigator.

The DMC is supported in its mission of safety and compliance by experienced ICTR staff to provide administrative assistance, experienced members representing a diversity of backgrounds, skills and knowledge, and the use of the ICTR OnCore clinical research management system which allows more efficient tracking of protocols and protocol subjects. In providing oversight for the conduct of this study, the ICTR DMC meets annually during the length of study. Additional meetings are scheduled as determined by the DMC or as requested by the PI. The DMC members review protocol-specific reports created by statisticians that serve a non-voting member role on the DMC using data pulled from the ICTR OnCore clinical research management system. These standard reports include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events.

An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

ICTR Study Monitoring Service (SMS)

While many institutions involved in clinical research conduct various types of quality assurance reviews and audits, UW ICTR is one of the few institutions to offer independent Study Monitoring Services, a robust academic equivalent to the Industry Contract Research Organization (CRO) standards for ongoing study monitoring.

The Study Monitor Services have been contracted for in the placental study, and include the conduct and follow-up of monitoring visits throughout the life cycle of the study (e.g., Study Initiation Visit, Interim Monitoring Visits, and Close-Out Visit). Study monitoring visits occur off-site (remotely) and/or on-site at a frequency necessitated by the protocol risk and complexity. For this study, UW ICTR SMS personnel will conduct a Study Initiation Visit (SIV) with the University of Wisconsin's research personnel in person after IRB approval was confirmed and before enrollment of any subjects into the study.

The SIV will included a detailed review of the protocol, good clinical practice guidelines, and data management expectations of the research team at the study site and SMS personnel.

Following the Study Initiation Visit (SIV), SMS personnel will routinely conduct ongoing Interim Monitoring Visit (IMVs) for all data collection sites, either on-site, remotely or a combination of both, following enrollment of the first subject(s) and throughout the duration of the study. During the IMVs, the monitor will review study materials, including but not limited to: regulatory files, consent forms, case report forms, and drug accountability logs. SMS personnel will review compare the electronic data to that of the primary source documents and case report forms (described above). UW ICTR SMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

Monitoring consists of full or partial review of study records, depending on the risk level and observed compliance. As such, during their monitoring activities, UW ICTR SMS personnel plan to review all (100%) of the study-related subject records for 10% of the enrolled subjects. SMS personnel could increase the percentage of study or subject records to be reviewed if warranted by the ongoing monitoring findings. The study monitor(s) work with the ICTR DMC statistician to conduct periodic central data reviews, with follow-up conducted by the study monitors for any data discrepancies identified.

The SMS conduct interim-monitoring visits (IMV) to insure compliance and safety. The first IMV will be scheduled following the enrollment of the first 1-2 subjects. Subsequent IMVs will be scheduled to occur approximately quarterly. The schedule may vary based on study enrollment rate. Unscheduled visits may be conducted based on reports or evidence of potential noncompliance, significant increases in subject enrollment rates, or changes in protocol/personnel and training activities. SMS service agreement is attached to the ARROW application.

ASSESSMENT OF SAFETY

Adverse Event (AE)

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for adverse event monitoring and reporting. The CTCAE v5.0 is the default version available in the ICTR OnCore system and applied by default in the electronic adverse event log.

This information can also be downloaded from the CTEP home page (http://ctep.info.nih.gov/CTC4/ctc_ind_term.htm).

The severity of the event will be graded using the CTCAE. In addition, for comparison to the CTCAE, adverse events will be tabulated using a 3-level schema as defined below:

Mild: event may be noticeable to patient; does not influence daily activities; usually does not require intervention.
Moderate: event may be of sufficient severity to make patient uncomfortable; performance of daily activities may be influenced; intervention may be needed.
Severe: event may cause severe discomfort; usually interferes with daily activities; patient may not be able to continue in the study; treatment or other intervention usually needed.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs.

Next, it will be determined by the study physician(s) whether the event is expected or unexpected and if the AE is related to the intervention or procedure or administer the intervention. With this information, it will be determined whether an AE should be reported as an expedited report in addition to submission via routine clinical data.

Expedited AE reporting may require e-mail notification, phone, or fax submission of a written report as directed below. All expedited AE reports will be submitted to the FDA (if applicable) and the IRB of record, the UW Health Sciences Institutional Review Board (HSIRB) in the case of this study.

Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any phase of the study (i.e., screening, admission, treatment, or follow-up) that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization (more than 24 hours)
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Unanticipated Problem (UP) Definition

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the

nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places participants or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

Assessment of Attribution

The PI or sub-investigator study physicians will assess adverse events to determine the attribution or relatedness to the study procedures and/or intervention. When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definitely Related: An AE categorized as Definite is clearly related to the intervention. If the timing of the AE is definitely consistent with the exposure to the study intervention and it, is most likely that the AE was caused by the study intervention such as because a high occurrence of the AE was expected based on the study intervention materials? In this case, the PI may categorize the AE as definitely related.

Probably Related: An AE that is likely related to the use of the drug. A Probable AE is likely related to the intervention. If the timing of the AE is consistent with the exposure to the study intervention and it is more likely that the AE was caused by the study intervention than not, the PI may categorize the AE as Probable.

Possibly Related: An AE that may be related to the use of the drug. If the timing of the AE is reasonably consistent with the exposure to the study intervention, and there is another cause of the AE that could be equally likely, the PI may categorize the AE as Possible.

Unlikely Related: An Unlikely AE is one that is doubtfully related to the intervention. The coincidence of the AE with the exposure of the investigational product or intervention should be assessed. An AE that continued while the intervention was interrupted or stopped, or if the AE resolved while the intervention continued, may be categorized as Unlikely. If there is another more likely cause of the AE, the PI may determine that the AE was unlikely related to the study intervention.

Not Related/Unrelated: An Unrelated AE is one that is clearly NOT related to the intervention. An AE may be considered Unrelated if the subject did not receive the study intervention or if there is another obvious cause of the AE (for example, a car accident or other disease/condition).

Adverse Events of Special Interest

Adverse events pertaining to the subject (mother) or neonate child occurring after the signing of consent until 6 weeks post-delivery, will be collected. Conditions that are

routinely encountered by obstetricians or pediatricians, such as C-section or infant jaundice, will be recorded on the adverse event log, but will not be reported (i.e. entered into OnCore) per clinical investigator's judgement. All adverse events meeting the HS-IRB reportable event requirements will be entered into OnCore, regardless of being considered a routine condition.

Adverse events that are expected in pregnancy and assessed as not related/unrelated to the protocol will not be reported to the ICTR DMC and entered into OnCore. These events include but are not limited to nausea and vomiting, dizziness, abdominal discomfort, back pain, vaginal discharge, and Braxton Hicks contractions.

Given the exclusion criteria and MRI screening, we do not anticipate any major events related to the MRI procedure. However, it is possible that patients report claustrophobia or anxiety in the large bore MRI machines. This may potentially require that we reduce the BMI cutoff from 39.9 Kg/m^2 to a lower value for the purpose of our study examination. The adverse response and claustrophobia concerns, even in a wide bore MRI research equipment, is one of the reasons we are choosing the BMI range of 18.5-39.9 Kg/m^2 for our study purposes.

Any planned hospitalizations for the delivery will not be reported as an SAE, but if any AE occurs during delivery or if the hospitalization is lengthened due to safety concerns this will be reported.

Genetic conditions, birth defects, or cardiac defects not recorded or suspected prior to consent will be documented as adverse events.

Any event may be documented and followed for up to 1 year post-delivery upon investigator's discretion.

Serious Adverse Event Reporting Requirements

Adverse Events that are:	**Notify HS IRB**	**Notify DMC**	**Notify FDA** (events related to Ferumoxytol-MRI only)**
Serious Suspected/Related* Unexpected	Within 14 business days	Within 14 business days	Notify FDA and all participating institutions as soon as possible, but no later than 15 calendar days after learning of the event
Serious Life threatening or Fatal Suspected/ Related* Unexpected	Within 1 business day (24 hours) of learning of the event.	Within 1 business day (24 hours) of learning of the event.	Within 7 calendar days of learning of the event

* The UW-Madison HSIRB requires immediate reporting of serious adverse events that are probably or definitely related, whereas the FDA requires reporting of these events that are possibly, probably or definitely related. Therefore if an event is reported to the HSIRB, the event will also be reported to the FDA.

Reporting requirements to the ICTR Data Monitoring Committee

All recorded AEs will also be available to the ICTR DMC by completing the AE/SAE forms in OnCore. The reporting requirements are consistent with those of the HS IRB, as well as the same timeframe. Once entered into OnCore, an automatic notification of an SAE will be sent to the ICTR DMC as an automated notification.

Study Stopping Guidelines

The study will be stopped or significantly changed if at least one of the following occurs:

- More than 10% of subjects experience severe claustrophobia or severe anxiety related to the MRI procedure
- For subjects receiving ferumoxytol, the study will be stopped or significantly changed if 2 subjects have an anaphylactic reaction

Subject Stopping Guidelines

If the subject experiences any adverse events or any issues arise that may affect the subject's safety, the subject will be withdrawn from the study.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- There is evidence of progressive disease or unacceptable toxicity

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